Impact of sinus surgery on pseudomonal airway colonization, bronchiolitis obliterans syndrome and survival in cystic fibrosis lung transplant recipients

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Impact of Sinus Surgery on Pseudomonal Airway Colonization, Bronchiolitis Obliterans Syndrome and Survival in Cystic Fibrosis Lung Transplant Recipients

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Key Words
Bronchiolitis obliterans syndrome · Cystic fibrosis · Lung transplantation · Paranasal sinus surgery · Pseudomonal airway colonization · Survival after lung transplantation

Abstract
Background: Lung transplantation (LTx) is a therapy for patients with cystic fibrosis (CF) end-stage lung disease. Pseudomonal airway colonization (PAC) is common in CF. ***Objectives:*** We investigated the influence of post-transplant sinus surgery and daily nasal douching on PAC after LTx and the influence of PAC on survival and bronchiolitis obliterans syndrome (BOS). ***Methods:*** CF patients transplanted at our centre were included (November 1992 to December 2009). Clinical data, including microbiological data before and after LTx were collected. Survival and BOS following LTx were compared for CF recipients with and without PAC by Kaplan-Meier statistics and Cox regression analysis. ***Results:*** Ninety-four CF patients were transplanted, of whom 82 (87%) underwent sinus surgery after transplantation, and 65% of 66 patients with pre-transplant PAC had persistent PAC after transplantation. Upper and lower PAC is related. Patients without PAC after transplantation had a significantly better survival rate, and BOS was less frequent with a later onset. PAC was the only significant parameter for the development of BOS stage 2 in the multivariate analysis for cytomegalovirus infection, acute rejection and PAC. ***Conclusions:*** Sinus surgery and daily nasal douching reduced PAC in LTx recipients. Absence of post-transplant PAC had a positive impact on post-transplant survival and the development of BOS.

Introduction

Bilateral lung transplantation (LTx) offers true survival benefits to patients with end-stage cystic fibrosis (CF) lung disease if selected appropriately and timed well [1]. Long-term survival of lung transplant recipients is primarily limited by late allograft dysfunction and depends on careful post-transplant management, including the

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prevention and treatment of airway infections [2]. Persistent post-transplant pseudomonal airway colonization (PAC) could be a risk factor for bronchiolitis obliterans syndrome (BOS), specifically for CF patients [3, 4]. Sinus surgery in combination with routine nasal care may be beneficial in this case [1, 5]. Nevertheless, there is an ongoing controversy about the impact of sinus surgery combined with daily nasal douching in CF lung transplant recipients and about post-transplant survival and the development of BOS.

We systematically evaluated CF patients undergoing LTx at our centre and analysed the potential impact of routinely performed post-LTx sinus surgery combined with daily nasal douching on PAC after LTx. We also examined the influence of PAC on survival and the development of BOS.

Materials and Methods

Between 1992 and 2009, 94 patients with CF underwent LTx at the University Hospital Zurich. One patient with simultaneous heart-lung transplantation was not included. LTx recipients were followed until the end of June 2011. There was a minimal follow-up of 18 months per patient.

Candidates for LTx were carefully selected following the international guidelines of the International Society for Heart and Lung Transplantation Pulmonary Scientific Council [6]. The transplantation type was a sequential bilateral LTx, which was performed with extracorporeal membrane oxygenation support if one lung ventilation or clamping of the pulmonary artery was not tolerated [1].

The standard protocol of immunosuppression (cyclosporine, azathioprine or mycophenolate mofetil and prednisolone) and induction therapy (antithymocyte globuline or basiliximab) was followed as described by Speich et al. [7]. Based on the sputum cultures, all patients underwent treatment with a combination of at least two antibiotics for *Pseudomonas aeruginosa* (PA) for at least 2 weeks. Further prophylactic therapy was performed with cotrimoxazole, acyclovir/valacyclovir, oral itraconazole and nebulized amphotericin B. Additionally, recipients with CF received a nebulized antibiotic therapy with colistin as prophylaxis (until negative PA cultures in microbiological samples of the nose as well as of the lung were achieved).

Sinus surgery was performed after recovery from transplantation [mean days after LTx 36, 95% confidence interval (CI) 24–47] as previously described and consisted of an endoscopic fronto-spheno-ethmoidectomy [5, 8]. Daily nasal douching with an isotonic saline solution was started on the second day after surgery and continued until the end of follow-up.

Surveillance bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies was performed in the first year after transplantation (normally every month for the first 6 months and when clinically indicated afterwards), along with nasal endoscopy with aspiration of sinus secretions. The BAL of 200 ml sterile normal saline was normally performed in the right middle lobe or the lingula. The material from the BAL and the sinus aspirates were sent for microbiological analysis according to standard methods [9]. The material was assessed semi-quantitatively; $\geq 10^4$ colony-forming units/ml bacteria in the sinus aspirate were considered as significant [10]. In BAL, any bacteria growth was recorded as significant.

The bacteriological results were evaluated according to the growth of CF-relevant pathogens in cultures, i.e. PA, *Staphylococcus aureus*, *Stenotrophomonas maltophilia* (Steno), *Achromobacter (Alcaligenes) xylodoxidans* (Achromo) and *Burkholderia cepacia complex* (BCC). The histological criteria for acute rejection in the transbronchial biopsies were applied as described elsewhere [11]. Acute cellular rejection episodes with a grade ≥A2 were treated with a 3-day course of methylprednisolone (at least 5 mg/kg body weight on day 1, followed by 2 days of at least 2.5 mg/kg body weight).

Patients with BAL cultures positive for the above pathogens received a standard antibiotic treatment according to pre-transplant microbiological finding and resistance test. Patients with PA were treated according to antimicrobial susceptibility testing with at least one β-lactam or ciprofloxacin and with an aminoglycoside (or colistin intravenously) if renal function permitted for at least 14 days. Persistent PAC [nasal colonization (PNC) and pulmonary colonization (PPC)] was defined as persistent positive cultures for PA (and BCC) after a trial of eradication (normally one course of intravenous antibiotics) in the upper and lower airways.

The diagnostic criteria for BOS were applied as described elsewhere [2]. In the late 1990s, patients with development of BOS 1 were treated with a macrolide (clarithromycin), and since the early 2000s, this treatment was started even with BOS 0-p.

Estimated pre-LTx survival was calculated according to Liou et al. [12].

The institutional review board of the University Hospital Zurich (Kantonale Ethikkommission Zurich) approved this retrospective study (EK-818).

Statistical Analysis

Descriptive statistics were used, and the mean and 95% CIs were generally given. Two groups were formed: group A, patients without PA 1 year after transplantation (without PAC), and group B, patients with persistent PA 1 year after LTx, including 2 patients with BCC (with PAC). Twelve patients without sinus surgery and 3 patients with insufficient data (all chronically infected with PA before transplantation) are counted as a failure of PA eradication (group B). The Mann-Whitney U test and Fisher's exact test with a significance level set at $p < 0.05$ were used to compare between the two groups. Survival and BOS were analysed using Kaplan-Meier estimates, and the log-rank test was used to compare the two groups for survival and BOS (all stages). Cox regression was applied to model the relation between occurrence of BOS (stages 1 and 2) and cytomegalovirus (CMV) infections, cumulative rates of acute rejection episode in the first year (no acute rejection and at least one or more acute rejection episode as defined by International Society for Heart and Lung Transplantation grade A2) [11] and PAC. IBM® SPSS® Statistics version 19 was used for the statistical analysis.

Results

Study Population

Ninety-four patients with CF were evaluated for LTx at our centre since its establishment in 1992 until December 2009. Patient demographics are displayed in table 1. The majority of the patients were chronically infected with PA, 2 patients were infected with BCC and 6 patients had an *S. aureus* infection alone. The estimate for survival without LTx was low (5-year survival of 33%). The 1- and 5-year survival rates after LTx were 85 and 67%, respectively. Twenty-four patients (25.5%) had a follow-up of <2 years. Freedom from BOS 1 after 5 years was 76%.

Twelve patients had no sinus surgery: 2 patients suffered from early graft dysfunction with low post-transplant forced expiratory volume in 1 s (2%), 8 patients (9%) died early after transplantation (early graft failure or multi-organ failure due to sepsis) and 2 patients (2%) were inoperable due to early post-transplant infection.

Eradication of PA and Other Bacteria

Thirty-five percent of the 66 patients with pre-transplant PAC had successful PA eradication in the sinuses and lungs (table 2). Thirty-eight percent had persistent PPC and 27% had only PNC (resulting in a total of 65% with persistent PNC of the pre-transplant PPC). No patient had PPC alone after transplantation.

Overall, a total of 40% were without PAC (PPC and PNC) 1 year after LTx (table 3). No patient without PAC before transplantation acquired PA after transplantation (over the entire observation time).

The 4 and 5 patients with Achromo and Steno, respectively, were successfully eradicated after LTx. One of the 2 patients with BCC had persistent colonization of the airways (nasal and bronchial), and the other had transient BCC in the upper and lower airways during the first year after LTx, which was successfully eradicated over the entire observation time of >10 years.

Survival and BOS

The 38 patients without PAC (PPC and PNC) after transplantation (group A) had a significantly better survival rate compared to patients with persistent PAC (table 4; fig. 1). No difference was observed for BOS 0-p, but BOS 1 and 2 were significantly less frequent in the group without PAC than in the group with PAC (fig. 2). The impact of PAC on the development of BOS was only seen during the early post-transplant phase, and the mean time for the development of BOS was significantly earlier

Table 1. Baseline characteristics

Characteristics	n = 94
Gender, female/male	47/47 (50/50)
Age at LTx, years	26.8 [25.1–28.5]
Microbiology before transplantation	
Only *S. aureus*	6 (6)
PA	77 (82)
Achromo	4 (4)
Steno	5 (5)
BCC	2 (2)
Sinus surgery	82 (87)
Sinus surgery after LTx, days	26 [24–47]
Estimated 5-year survival without LTx[1], %	33 [30–36]
Follow-up, years	5.7 [4.8–6.6]
1-year survival, %	85 [78–90]
5-year survival, %	67 [60–73]
Freedom of BOS 0-p at 5 years, %	47 [42–52]
Freedom of BOS 1 at 5 years, %	76 [67–82]
Freedom of BOS 2 at 5 years, %	82 [74–88]
Freedom of BOS 3 at 5 years, %	88 [79–93]

Figures in parentheses are percentages; figures in brackets are 95% CIs.

[1] According to Liou et al. [12].

Table 2. Success and failure of PA and BCC eradication after sinus surgery (n = 66)[1]

	PNC		Total
	no	yes	
PPC			
No	23 (35)	18 (27)	41 (62)
Yes	0	25 (38)	25 (38)
Total	23 (35)	43 (65)	

Figures in parentheses are percentages. F test, p < 0.0001.

[1] Thirteen patients were excluded (9 without sinus surgery and 4 because of missing data).

Table 3. Free from PA and BCC after LTx (n = 94)

	After transplantation		Total
	no PA/BCC	PA/BCC	
Before transplantation			
No PA/BCC	15 (16)	0	15 (16)
PA/BCC	23 (24)	56 (60)	79 (84)
Total	38 (40)	56 (60)	

Figures in parentheses are percentages. F test, p < 0.0001.

Table 4. Survival and BOS for the two groups

	Group A	Group B	p
Patients	38 (40)	56 (60)	
Gender, female/male	22/16 (58/42)	25/31 (45/55)	n.s.
Age at LTx, years	26.3 [23.6–29.0]	27.1 [24.8–29.3]	n.s.
CFTR genotype			
Unknown	1 (3)	11 (19)	
Known	37 (97)	47 (81)	
dF508 homozygous	23 (62)	28 (60)	
dF508 heterozygous	13 (35)	14 (30)	n.s.
Without dF508	1 (3)	3 (10)	
Estimate survival without LTx, %	34 [29–39]	32 [29–36]	n.s.
Follow-up, years	5.7 [4.4–7.1]	5.7 [4.4–7.0]	n.s.
1-year survival, %	92 [79–97]	80 [70–87]	n.s.
5-year survival, %	86 [72–93]	57 [49–64]	0.007
Acute rejections (grade A2) during follow-up[1]			
None	14 (50)	17 (44)	
Once	8 (29)	15 (36)	n.s.
Twice or more	6 (21)	8 (20)	
CMV infection ≥1	3 (8)	4 (7)	n.s.
Clarithromycin, yes/no	10/28 (27/74)	25 (45/55)	n.s.
Time after LTx for BOS 0-p, years	3.7 [2.4–4.9]	3.8 [2.8–4.8]	n.s.
Freedom of BOS 0-p at 5 years, %	49 [41–58]	46 [39–53]	n.s.
Time after LTx for BOS 1, years	5.4 [4.1–6.8]	4.7 [3.5–5.9]	
Freedom of BOS 1 at 5 years, %	85 [68–93]	69 [59–78]	0.056
Time after LTx for BOS 2, years	5.6 [4.3–6.9]	4.9 [3.7–6.1]	
Freedom of BOS 2 at 5 years, %	93 [78–98]	74 [63–80]	0.025
Time after LTx for BOS 3, years	5.6 [4.3–7.0]	5.3 [4.1–6.5]	
Freedom of BOS 3 at 5 years, %	93 [77–98]	84 [72–91]	n.s.

Figures in parentheses are percentages; figures in brackets are 95% CIs. Group A: no PA or BCC at evaluation (15 patients) or successful eradication of PA (nasal and bronchial) 1 year after transplantation (23 patients). Group B: chronic infection with PA at 1 year (including 1 patient with BCC). n.s. = Not significant; CFTR = CF transmembrane conductance regulator.

[1] Twenty-six patients without transbronchial biopsies.

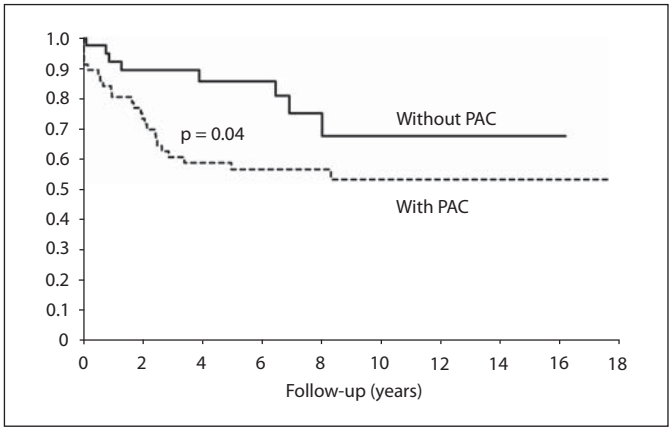

Fig. 1. Survival in patients without PA and BCC 1 year after LTx (without PAC) compared to infected patients with PA or BCC (with PAC). The log rank test was used.

in the PAC group (table 4). Gender, age, pre-transplant prognosis without LTx, CF transmembrane conductance regulator genotype and episodes of acute rejections and CMV infections after transplantation were equally distributed in both groups. In the multivariate Cox regression analysis, persistent PAC was the only significant risk factor for development of BOS 2 with a hazard ration of 3.79 (95% CI 1.10–13.11; p = 0.035), and for BOS 1, a strong trend was observed (hazard ratio 2.31, 95% CI 0.98–5.45; p = 0.055).

In 18 of the 28 patients with BOS 1, BAL was available at the time of diagnosis of BOS 1 (13 patients with PAC and 5 without PAC). In patients with persistent PAC, there was a tendency of more neutrophilic alveolitis than in patients without PAC (54 vs. 40%).

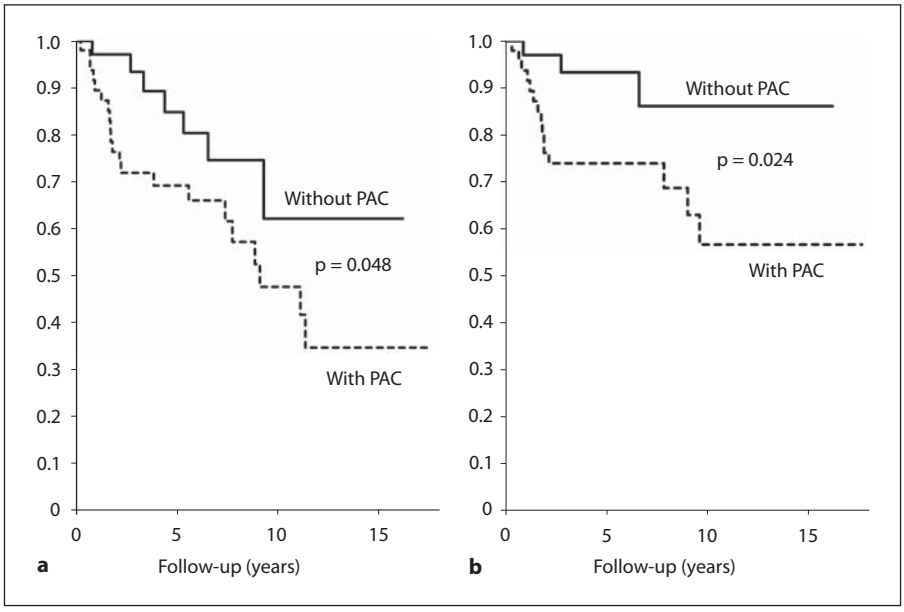

Fig. 2. Freedom of BOS 1 (**a**) and BOS 2 (**b**) in patients without PA and BCC 1 year after LTx (without PAC) compared to infected patients with PA or BBC (with PAC). The log rank test was used.

Discussion

We report three major findings: (1) the growth of *Pseudomonas* in cultures of paranasal sinus aspirates and BAL after LTx was highly correlated; (2) one third of patients with pre-transplant PAC were successfully eradicated; and (3) patients with persistent PAC were at higher risk for the development of BOS and had a lower survival rate after LTx.

Relation of PNC and PPC

Pseudomonal growth in cultures of sinus aspirates is significantly related to bacterial growth in BAL, indicating a lower risk for lung allograft infection and complications in patients with successful eradication in the sinuses. These findings are consistent with those of our previous study [5] and other authors [13–16] who recognized a similarity between the bacterial flora in the sinuses and the lower airways, suggesting cross-infection. Roby et al. [13] further observed that bacteria were more likely to be found in the sinuses and to descend into the lower airways at later stages of the CF disease. Special attention should be attributed to the eradication of bacteria in the sinuses, which requires endoscopic sinus surgery *and* daily nasal douching with isotonic saline solution. The authors who did not include daily nasal care in their protocol observed no significant reduction in bacteria type or bacterial recolonization [17, 18].

Success of Eradication

There are only a few studies that examine the success rate of *Pseudomonas* eradication in post-transplant recipients [3, 5, 17, 19]. In a larger study, including 87 patients with pre-transplant sinus surgery, 82 and 87% had persistent PNC and PPC, respectively [17]. In our previous study, PNC persisted in 46% [5]. In the current study, persistent PNC was higher (65%) for the 66 patients with pre-transplant PAC. One reason for this finding could be the more rigid definition of PAC. Nevertheless, with our protocol of post-transplant sinus surgery, which was followed by strict nasal douching, 62% of patients with pre-transplant PAC achieved persistent PA eradication in the lower airways. All patients with pre-transplant Gram-negative bacilli, other than PA and BCC (Achromo and Steno), were successfully eradicated after LTx. One patient with BCC had a persistent BCC infection after transplantation (in the upper and lower airways), and another had transient BCC colonization with successful eradication over time (at the 10-year follow-up). No patient without PAC before transplantation developed pseudomonal infection after transplantation. One reason for this finding could be the strict post-transplant segregation concept of our programme (prevention of cross-infection).

PAC, Survival and BOS

The patients with persistent PAC (PNC and PPC) had a higher mortality and BOS rate compared to the *Pseudomonas*-negative patients after transplantation. This find-

ing is consistent to those of other groups [3, 19–21]. Leung et al. [17], who followed a protocol of pre-transplant sinus surgery, observed no significant benefit to long-term survival relative to other comparable cohorts of CF patients with no sinus surgery. However, their protocol did not include daily nasal care, which is essential to achieving the persistent eradication of pathologic bacteria in the sinuses. Post-transplant PAC is associated with neutrophilic airway inflammation, leading to a self-perpetuating cycle of airway damage and, subsequently, airway remodelling [3, 22]. Neutrophilic airway inflammation plays an important role in chronic allograft dysfunction [23], and persistent PAC is assumed to be a risk factor for BOS. In our cohort, there was a tendency of more neutrophilic alveolitis in patients with PAC. Nevertheless, the sample size was too small for a valid statement.

The presence of pan-resistant, Gram-negative bacilli (other than BCC) is likely a risk factor for worse overall survival after LTx [19, 21]. In our cohort of 94 patients, only a few patients had pan-resistant, Gram-negative bacilli. All patients with *Achromobacter* and *Stenotrophomonas* successfully eradicated these bacteria after transplantation, and the survival rates were even better than for patients with persistent PAC after transplantation.

We found no significant influence of acute rejection and CMV infections for the development of BOS, and persistent PAC was the only risk factor in the multivariate Cox regression analysis for development of BOS 2. One reason for this finding could be the more rigid protocol of post-transplant management with regular monthly bronchoscopic evaluation for acute rejections (and infections) and early treatment of rejection and the establishment of prophylactic concepts against CMV infections from the beginning of our LTx program, as previously described [23]. As a consequence of our therapeutic concept of starting macrolide treatment when lung function impairment is detectable (currently in the case of BOS 0-p), and in view of the fact that a strong trend of development of BOS 1 was found in patients with PAC, more of these patients received macrolide treatment (table 4). Nevertheless, the treatment with macrolides had no impact on survival (data not shown).

Our study has several limitations. First, this is a retrospective study, and we did not perform a randomized controlled trial to show the impact of sinus surgery (and regular nasal douching) in post-transplant CF patients. Nevertheless, since our establishment of the lung transplant programme in 1992, we have become convinced that freedom from PAC must be a goal of post-transplant management. To this end, we established the concept of regular post-transplant surgical revision of the sinuses to have the best possibility of reducing the pseudomonal load in the sinuses. Second, we did not look for all confounders, which could have influenced survival and particularly the development of BOS. Lymphocytic bronchitis/bronchiolitis are recognized as classic immunological risk factors [24, 25], and other non-immunological risk factors have been proposed, such as ischaemic reperfusion, early non-specific bronchial hyperresponsiveness, donor and recipient age, graft ischaemic time, gastro-oesophageal reflux and bacterial/fungal/non-CMV viral infections [26]. Due to our small cohort, a reliable statistical analysis for these risk factors was difficult.

New concepts are appearing on the horizon. Hypothetically, at least two different BOS phenotypes can be distinguished; apart from the neutrophilic type, which is responsive to azithromycin, there is another type without neutrophilic inflammation [24]. While the neutrophilic type (probably triggered by PAC) starts early after transplantation (often in the first post-operative year), the other type is primarily diagnosed later on. This observation could be the reason we found significant development of BOS in patients with persistent PAC in the early post-transplant phase but a similar survival curve later on.

In conclusion, our study highlights the importance of early post-transplant eradication of pre-transplant PAC.

Sinus surgery and daily nasal douching reduced bacterial infection of the allograft in CF lung transplant recipients and had a positive impact on post-transplant patient survival and BOS.

Financial Disclosure and Conflicts of Interest

None of the authors has a conflict of interest regarding the submitted study.

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